Advantame

Chemical and Technical Assessment

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1. Summary

Advantame was not previously evaluated by JECFA and it has been recommended for priority evaluation at the 44th Session of the Codex Committee on Food Additives (CCFA) (FAO/WHO, 2012). This Chemical and Technical Assessment document is based on data and information submitted by Ajinomoto Co., Inc., in the dossier dated December, 2012 (Ajinomoto, 2012).

Advantame (ANS9801 - laboratory code name) is an N-substituted (aspartic acid portion) derivative of aspartame that is intended for use as a non-nutritive sweetener. Advantame has been demonstrated to be approximately 100 times sweeter than aspartame and approximately 37000 times sweeter than sucrose. Advantame is manufactured via a chemical synthesis.

Approval for the use of advantame as a Schedule 2 food additive [permitted to Good Manufacturing Practices (GMP) in processed foods] in Australia/New Zealand has been recently issued by Food Standards Australia New Zealand (FSANZ) (FSANZ, 2011). INS No. 969 has been assigned to advantame at the 45th Session of the CCFA in 2013 (FAO/WHO, 2013)

New tentative specifications were prepared at the 77th JECFA (2013) and published in FAO JECFA Monographs 14 (2013) requesting information on:

- Suitability of the head space GC method (using appropriate dissolution solvent) for determination of residual solvents published in the “Combined Compendium of Food Additives Specifications, Vol. 4” and data, in a minimum of 5 batches, using the method,
- An alternative/improved HPLC method for the assay of advantame and advantame-acid using a standard curve,
- Additional data and analytical methods for determination of palladium and platinum,
- Information on the purity and availability of the commercial reference standards used in the assay of advantame and advantame-acid

2. Description

Advantame (N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl]-α-aspartyl]-L-phenylalanine 1-methyl ester, monohydrate; CAS No.: 714229-20-6) is an N-substituted (aspartic acid portion) derivative of aspartame that is similar in structure to neotame, another N-substituted aspartame. Advantame has a molecular formula of C24H30N2O7·H2O and a corresponding molecular weight of 476.52 g/mol (monohydrate). The final advantame product consists of not less than 97.0% and not more than 102.0% of C24H30N2O7 (anhydrous).

Advantame appears as a white to yellow powder, with a sweet taste. At 25°C, advantame was shown to be very slightly soluble in water (0.099 g advantame/100 ml water) and sparingly soluble in ethanol (1.358 g advantame/100 ml ethanol), with solubility increasing in both solvents with heating.

The structural formula for advantame is presented in Figure 1.
3. **Method of manufacture**

Advantame can be produced via a three-step synthetic chemical process, beginning with the production of the principal manufacturing intermediate, 3-hydroxy-4-methoxycinnamaldehyde (HMCA), from water, sodium hydroxide, and isovanillin in methanol. This is followed by selective hydrogenation of HMCA to form 3-(3-hydroxy-4-methoxyphenyl) propionaldehyde (HMPA). The final step involves N-alkylation of aspartame (L-α-aspartyl-L-phenylalanine methylester) with HMPA to form advantame.

Alternatively, high-purity HMCA can be sourced externally, and thus be considered the starting material for the production process.

Methanol and isopropyl acetate or ethyl acetate are used as reaction solvents and re-crystallisation solvents in the preparation of advantame. The sponsor additionally informed the Committee that isopropyl acetate is no longer used in the production of advantame.

4. **Characterization**

4.1 **Composition**

The final advantame product consists of not less than 97.0% and not more than 102.0% of C₂₄H₃₀N₂O₇ (anhydrous). Specifications proposed by the sponsor include limits for N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl]-α-aspartyl]-L-phenylalanine (advantame-acid) and other related substances of not more than 1.0 and 1.5% of the product, respectively, limits for the residual solvents methanol and ethyl acetate at 500 mg/kg each, a limit for inorganic substances (residue on ignition) of 0.2%, and a limit for lead of 1 mg/kg. The sponsor had also initially proposed a limit of 2,000 mg/kg for the residual solvent isopropyl acetate, but this specification has been removed from the tentative specification based on the indication of the sponsor that isopropyl acetate is no longer used in the manufacture of advantame.

4.2 **Possible impurities (including degradation products)**

Possible impurities of advantame include: (i) substances related to advantame; (ii) production intermediates, including HMCA, HMPA, HMPA-alcohol, di-HMPA, and isovanillin; (ii) residues of solvents (i.e., isopropyl acetate/ethyl acetate and methanol) used in the manufacturing process of advantame or their hydrolysis products (i.e., methyl acetate and 2-propanol); (iv) residues of the hydrogenation catalysts (i.e., palladium on aluminium oxide and platinum on carbon) and (v) inorganic impurities and heavy metals (lead).

**Substances related to advantame**

Several related substances of advantame have been identified in the final advantame product as manufacturing impurities. Specifically, batch analysis was conducted on 12 lots of advantame for related substances. For each sample lot, analysis was conducted using two high performance liquid chromatography (HPLC) methods. Using the first method (“old method”), co-elution of some
related substances was identified, thus the original method was modified to increase the sensitivity and allow for better separation of the related substances.

Using the modified method, a total of 27 related substances were identified in advantame. Of these, only 16 peaks were identified in amounts that were quantifiable. The majority of the related substances were found only in trace amounts in the sample lots or were not detected at all in some samples. Depending on the sample lot, values ranged from 0.55 to 1.39% for total related substance content.

Of the 16 quantifiable peaks, five substances were present in the final advantame material at levels above 0.1% (up to 0.41%) and were fully characterized (i.e., principal substances related to advantame) as the following:

- L-α-aspartyl-L-phenylalanine methylester (Aspartame);
- N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl]-α-aspartyl]-L-phenylalanine (advantame-acid);
- N-[N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-α-L-aspartyl]-α-L-aspartyl]-L-phenylalanine 1-methyl ester (N-Alkyl-AAPM);
- N-[N-[3-(3-hydroxy-4-methoxyphenyl)pentyl]-α-L-aspartyl]-L-phenylalanine 1-methyl ester (9801-D); and
- N-[N-[3-(3-hydroxy-4-methoxyphenyl)heptyl]-α-L-aspartyl]-L-phenylalanine 1-methyl ester (9801-T);

The structural formulas of advantame-acid, N-alkyl-AAPM, 9801-D and 9801-T are presented in Figure 2.

![Figure 2. Structural formulas of advantame-acid, N-alkyl-AAPM, 9801-D and 9801-T](image)

The remaining 11 substances were identified consistently in very small quantities (below 0.1% in the final product). Substances identified in the final product at levels below 0.1% were not characterized. The peak corresponding to relative retention time (RRT) 1.24 was detected in one of the examined lots at 0.12%; however, because levels of RRT 1.24 were consistently below 0.1% in the remaining 11 lots, it too was not characterized. According to the sponsor, given the low levels at which these related substances occurred in the final product, combined with the low estimates of intake of advantame, full characterization of these related compounds was deemed unnecessary.
Production intermediates

Since advantame is produced synthetically via a series of chemical reactions, starting material (isovanillin), reaction intermediates (HMCA and HMPA), as well as reaction by-products (HMPA-alcohol, di-HMPA) could be present in the final product.

Although there are no analysis data for HMCA in the final batches of advantame, the sponsor reported that the presence of this potential impurity is routinely checked during the manufacturing process. Following the selective hydrogenation reaction to form HMPA, the presence of HMCA is determined by HPLC. If HMCA is present in detectable amounts (0.02%) in the HMPA filtrate (end of step 2), the HMPA filtrate is not used in the production process for advantame. Thus, the potential for HMCA carry-over into the final product is limited during the manufacturing process.

Similarly, the presence of isovanillin, HMPA, HMPA-alcohol, and di-HMPA was examined using HPLC during the development of the commercial production process. Analysis did not reveal any detectable levels of HMPA or its derivates in the production batches (detection limit of 0.02%). Hence, according to the sponsor, neither HMPA nor its derivatives are expected in the final product.

Solvent residues and their reaction by-products

The sponsor initially indicated that methanol and isopropyl acetate or ethyl acetate are used as reaction solvents and re crystallisation solvents in the preparation of advantame. Gas chromatographic analysis of 12 lots of advantame synthesized using methanol and isopropyl acetate was performed. While no peaks were apparent for methanol, the analysis did reveal peaks consistent with the presence of isopropyl acetate. The concentration of isopropyl acetate in the final product was determined to range from 307 to 1,907 mg/kg (mean of 573 mg/kg).

Since detectable levels of isopropyl acetate were identified in the advantame samples, limits for levels of residual solvents which may be present as a result of their use in the manufacture of advantame (methanol and isopropyl acetate or ethyl acetate) were originally included in the final product specification. However, as the sponsor has indicated that isopropyl acetate is no longer used in the manufacture of advantame, a specification for isopropyl acetate was not included in the tentative specifications for advantame prepared at the 77th meeting.

Additionally the potential for formation of methyl acetate and 2-propanol, which could arise as hydrolysis products or reaction by-products of the solvents also was examined. Analysis of the same 12 lots of advantame synthesized using isopropyl acetate as those analyzed for the potential presence of solvent residues, revealed no detectable levels of either methyl acetate or 2-propanol. Accordingly, specification parameters for the hydrolysis/reaction by-products of the solvents used during the synthesis were not included in the specifications for advantame.

Hydration catalysts

To examine the potential residual amounts of hydrogenation catalysts (e.g., palladium on alumina, platinum on carbon) in the final product, a number of manufacturing lots were analysed for platinum and palladium using inductively coupled plasma atomic emission spectrometry. Based on the analysis of 12 non consecutive lots, palladium was identified in the final product at levels up to 5.3 mg/kg; platinum was identified at levels up to 1.7 mg/kg. The sponsor did not propose inclusion of the limits for palladium and platinum in the advantame specifications with the following explanation.

The background intakes of palladium from food and drinking water have been suggested to be low with estimated daily intakes of 2 and 0.03 μg per day, respectively (WHO, 2002). Intake of platinum from its occurrence in the diet has been estimated to be 1.44 μg per day (WHO, 2000). With an estimated daily intake of up to 1.26 mg/kg body weight (bw) per day for advantame and a worst case palladium concentration of 5.3 mg/kg, exposure to palladium would be 0.0067 μg/kg bw per day from the consumption of advantame compared to 0.03 μg/kg bw per day from background
dietary sources. Furthermore, this estimate is likely an overestimates of palladium exposure from advantame since palladium levels in most lots were less than 0.2 mg/kg.

Using a similar calculation, the worst-case exposure of consumers to platinum would be 0.002 µg/kg bw per day compared to a background dietary exposure of 0.024 µg/kg bw per day.

**Inorganic matter and heavy metals**

Consistent with the proposed specifications for advantame, inorganic substances as measured by the test for residue on ignition are limited to a maximum of 0.2%. Lead is not permitted at concentrations above 1 mg/kg.

### 4.3 Rationale for proposed specifications

The proposed tentative specifications for advantame are intended to define the identity of the final product and limit levels of potential impurities.

Purity of the final food additive is established by determination of advantame content, on anhydrous basis (i.e., not less than 97.0% and not more than 102.0%). Identity of the material is verified by visual inspection (white to yellow powder) and comparison to an infrared (IR) absorption spectrum for the reference standard. Limits for advantame-acid (not more than 1.0%), a potential reaction by-product, as well as a degradation product of advantame, and other substances related to advantame (not more than 1.5%) including aspartame, 9801-D, 9801-T, and N-alkyl-AAPM also are proposed. Purity is further confirmed by determination of specific rotation.

The final purification of the advantame product, involves re-crystallisation from methanol, followed by washing of the crystals with methanol. Furthermore, in the final stages of advantame synthesis, the crude advantame crystals are produced by dissolution of the N-alkylation product concentrate in methanol and isopropyl acetate or ethyl acetate. The crude crystals are subsequently washed with isopropyl acetate/ethyl acetate. A specification parameter to limit levels of isopropyl acetate in advantame of not more than 2000 mg/kg is proposed based on batch analysis demonstrating levels of 307 to 1,907 ppm in the final product. Isopropyl acetate has been evaluated at the 25th JECFA (1981) and “no ADI” was allocated for the use as an extraction solvent and flavouring agent (JECFA No. 305). Under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) program regarding acceptable residual levels of solvents in drugs, isopropyl acetate is currently listed as a Class 3 solvent with an acceptable residual exposure of 50 mg per day (U.S. FDA, 1997, 2012). Considering that the estimated intake of advantame is equivalent to 1.26 mg/kg bw per day for advantame and the worst case isopropyl acetate concentration is 1,907 ppm, exposure to isopropyl acetate from advantame would be considerably lower (0.0024 mg/kg bw per day or 0.14 mg per day). For methanol and ethyl acetate, which were not detected in the analyzed lot samples, limits for the potential presence of these solvents of not more than 500 mg/kg are proposed. Ethyl acetate has been evaluated by JECFA as a carrier solvent and flavouring agent (JECFA No. 27) and an ADI of 0-25 mg/kg bw was established at the 11th JECFA (1967). For methanol JECFA ADI 'limited by GMP' for the use as an extraction solvent was established at the 14th JECFA (1970). The Committee was additionally informed by the sponsor that isopropyl acetate is not used anymore in the production of advantame, and, for this reason, the limit for isopropyl acetate was not included in the tentative advantame specifications.

Presence of inorganic matter is limited by the inclusion of a parameter for “residue on ignition” [not more than 0.2%, consistent with other related sweeteners (e.g., neotame)] and ‘lead’ (not more than 1 ppm, consistent with JECFA’s limits for heavy metals in food additives) (JECFA, 2002).

The Committee requested additional data and analytical methods for determination of residual levels of palladium and platinum.
4.4 Analytical methods


The assay method for advantame detection, as well as for substances related to advantame employed in the analysis of the bulk product is an internal single laboratory validated method based on HPLC coupled with an ultraviolet absorption detector. The Committee requested an alternative or improved HPLC method for the assay of advantame and advantame-acid using a standard curve and information on the purity and availability of the commercial reference standards.

The analytical method used to assay for residual solvents also is an internal validated method based on the gas chromatography (GC) with flame-ionization detector. The Committee requested information on the suitability of the head space GC method for determination of residual solvents published in the “JECFA Combined Compendium of Food Additives Specifications, Vol. 4”.

5. Functional uses

5.1 Technological functions

Advantame is intended for use as a non-nutritive sweetener in various food and beverage applications, and as a flavouring enhancer.

The taste profile and the effectiveness of advantame as a high-intensity sweetener, was examined through a series of sensory evaluations, with advantame provided at various concentrations and compared to sucrose-sweetened water or aspartame-sweetened water. Depending on the particular application (sucrose equivalencies of 3 to 14%), advantame has been demonstrated to be approximately 70 to 120 times sweeter than aspartame and 7,000 to 48,000 times sweeter than sucrose. At 6% SE the relative sweetness potency of advantame compared to aspartame in water was greater than 116 times the sweetness potency of aspartame or approximately 37,000 times sweeter than sucrose. At a sucrose equivalence of 11% (consistent with the typical sweetness of carbonated beverages), advantame was 100-fold sweeter than aspartame that equates to about 20,000 to 37,000 times sweeter than sucrose. The high sweetness potency of advantame permits it to be used as a sweetening agent in various food and tabletop products at levels far below those of sucrose and other high-intensity sweeteners currently on the market.

Furthermore, advantame was demonstrated to have a similar sensory profile to aspartame, especially at high concentrations with a dominant sweet flavour, while perceived intensities for bitter and sour flavours were very weak. Advantame also was demonstrated to perform very well as a sweetener in coffee (hot and warm), iced tea, and powdered beverage formulations. The functionality of advantame as a flavour enhancer also was examined and advantame was shown to possess favourable flavour enhancer properties in beverages.

Advantame is also a suitable sweetener alternative for diabetics as consumption of advantame was shown not to affect glucose homeostasis in healthy subjects, as well as in individuals with Type II diabetes.

5.2 Food Categories and Use Levels

Food categories and use levels proposed by the sponsor are listed in Table 1 in Annex 1

6. Reactions and Fate in Food

Stability and Degradation/Reaction Products

Advantame in dry form was shown to be stable under standard conditions of storage at 25°C/60% relative humidity (RH) for up to 60 months. Advantame also was shown to remain stable under
accelerated conditions (40°C/75% RH) for up to 6 months. Exposure of advantame samples to light during one and two weeks of testing demonstrated that advantame dry powder is stable in light.

The stability of advantame was examined in a number of real and simulated food and beverage matrices over a range of temperatures, pH values, and processing conditions, consistent with the 3-dimensional model that was developed and validated by Pariza et al. (1998) for the systematic examination of the stability of a novel food ingredient.

Specifically, the stability of advantame was tested in powdered preparations (tabletop sweetener product and dry powder beverage mix - low moisture, low heat, medium pH), carbonated drinks (non-aseptically processed - high moisture, low heat, low pH), heat-treated beverages (high moisture, medium to high heat, low pH), yellow cake (moderate moisture, high heat, medium pH), and yogurt (high moisture, medium heat, low pH) to cover most pH, temperature, and moisture extremes that the ingredient might be subjected to when added to the various food and beverage products under the proposed conditions of use. The stability of advantame also was examined separately in chewing gum. Additionally, in a study primarily designed to assess potential degradation products of advantame, stability also was examined in mock beverages.

For each food matrix, the stability was assessed by examining levels of advantame and in most cases (with the exception of yogurt), advantame-acid content. In addition, the functionality of advantame also was assessed in each of the studies following the specified storage periods by providing the advantame-containing food to a sensory panel.

Similar HPLC methods to the HPLC method developed for the analysis of the bulk material were developed and validated for the analysis of the advantame and advantame-acid content in the various food matrices.

Advantame (at a concentration of 446 ppm) in the form of a tabletop powder following 36 months of storage at 25±2°C/60%±5% RH was demonstrated to remain stable (86%) with a low formation of advantame-acid (11.89%).

Advantame was demonstrated to be stable in a lemon-flavoured dry powdered beverage mix following 12 months of storage under normal conditions (96.4%) and six months under intermediate and accelerated conditions (96.3%).

The chemical stability and functionality of advantame in a carbonated soft drink was evaluated following storage of up to 26 weeks at room temperature conditions. The results of the study demonstrate that approximately 50% of baseline advantame content was degraded in carbonated soft drinks following a 26-week storage period.

In order to assess the thermal stability of advantame, levels of advantame in an orange-flavoured beverage were examined before pasteurization and after the hot-pack process. Additionally, chemical stability and functionality of advantame were examined in the orange-flavoured drink following storage of up to 26 weeks at 25±2°C/60±5% RH. The results showed that short heat treatment caused less than 2% loss of advantame, whereas following the 26-week storage period, approximately 50% of advantame degraded, accompanied by an increase in the content of advantame-acid.

A thermal stability assessment of advantame was conducted on yellow cake batter before and after baking. Approximately 13.2% of the added advantame was lost during batter preparation and approximately 25.2% was lost during baking. The decrease in advantame levels was accompanied by increased levels of advantame-acid.

To assess the stability and functionality of advantame in prepared baked goods, yellow cakes containing advantame were prepared and stored at room temperature conditions for up to five days. Levels of advantame and advantame-acid in the based cakes were almost constant during the five-day storage period.
The chemical stability and functionality of advantame in yogurt was evaluated following refrigerated storage conditions of 5±2°C for five weeks. Following the storage period, levels of advantame declined to 76.2% of the advantame content at the start of the storage period. Although the degradation products were not be identified (due to interferences), they are expected to be advantame-acid and potentially HF-1 resulting from peptide hydrolysis by the two fermentation microorganisms, Streptococcus thermophilis and Lactobacillus bulgaricus.

To assess the stability of advantame in chewing gum, gum with added advantame was stored for a period of 27 weeks. At the end of the 27-week storage period, advantame levels declined from 377.03 mg/kg to 350.35 mg/kg, corresponding to a reduction of less than 10%. Reductions in advantame levels were accompanied by increased advantame-acid levels that at the end of the storage period increased to 12.64 mg/kg.

Advantame was considered to be functionally sweet in all tested food and beverages samples for the duration of the studies.

In mock beverages, the stability of advantame was shown to be pH-, temperature, and time-dependent, with levels of advantame decreasing with time, as well as lower pH values and higher temperatures.

The stability of advantame under various surrogate food conditions indicated that advantame likely slowly degrades under acidic conditions found in some beverage products. Possible degradation pathways for advantame and expected degradation products were elucidated based on the well-known degradation of the related high-intensity sweeteners, neotame and aspartame. The major and minor degradation pathways for advantame are outlined in Figure 3. Hydrolysis of advantame resulting in the formation of advantame-acid represents the major degradation pathway. Conversely, β-rearrangement comprises the minor degradation pathway.
In contrast to aspartame, advantame cannot form the diketopiperazine derivative, as there is no a free amino group to start the internal reaction of cyclisation.

Potential reaction with aldehydes (Maillard reaction)

Generally under the intended conditions of use and storage, some interactions between advantame and other food additives and food constituents may be expected. The possibility of advantame reacting in a Maillard-type reaction was considered. A number of factors specific to advantame chemistry and conditions present in food, minimize the potential for this to occur.

Fry and Stegink (1982) demonstrated that the rate of browning of a secondary amine (e.g., proline) was much slower than that of a primary amine and that amino acids with hydrophobic side chains reacted more slowly than other amino acids. Therefore the presence of a secondary amine and a hydrophobic side chain indicates that advantame should only have a slow Maillard reaction rate.

Potential formation of nitrosamines

The potential for the formation of N-nitroso compounds was assessed in 2 locations: (1) within foods and beverages (e.g., soft drinks and fruit-flavoured juices) where advantame may interact with the nitrite ion if present at a sufficient level in the beverages to form nitrosamines, and (2) within the stomach where the acidic environment (i.e., low pH) and the presence of nitrite from saliva provide a suitable site for nitrosation of advantame. This risk assessment provided by the sponsor demonstrates that the potential formation of N-nitroso advantame does not present a significant risk to the population as the theoretical formation of N-nitroso advantame is well below levels of nitrosamines typically present in meat products.

7. References


**Annex 1**

Table 1. Proposed food uses and use-levels for advantame

<table>
<thead>
<tr>
<th>Food Category No. and Food Category</th>
<th>Maximum Proposed Use-Level for Advantame (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.0 Dairy products and analogues, excluding products of food category 02.0</td>
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<tr>
<td>01.2 Dairy-based drinks, flavoured and/or fermented (e.g., chocolate milk, cocoa, eggnog, drinking yoghurt, whey-based drinks)</td>
<td>12</td>
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<tr>
<td>01.7 Dairy-based desserts (e.g., pudding, fruit or flavoured yoghurt)</td>
<td>20</td>
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<tr>
<td>02.0 Fats and oils, and fat emulsions</td>
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<tr>
<td>02.3 Fat emulsions mainly of type oil-in-water, including mixed and/or flavoured products based on fat emulsions</td>
<td>20</td>
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<tr>
<td>02.4 Fat-based desserts, excluding dairy-based dessert products of food category 01.7</td>
<td>20</td>
</tr>
<tr>
<td>03.0 Edible ices, including sherbet and sorbet</td>
<td>20</td>
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<tr>
<td>04.0 Fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds</td>
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</tr>
<tr>
<td>04.1.2.1 Frozen fruit</td>
<td>20</td>
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<tr>
<td>04.1.2.2 Dried fruit</td>
<td>20</td>
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<tr>
<td>04.1.2.3 Fruit in vinegar, oil, or brine</td>
<td>6</td>
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<tr>
<td>04.1.2.4 Canned or bottled (pasteurized) fruit</td>
<td>20</td>
</tr>
<tr>
<td>04.1.2.5 Jams, jellies, marmalades</td>
<td>20</td>
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<tr>
<td>04.1.2.6 Fruit-based spreads (e.g., chutney) excluding products of food category 04.1.2.5</td>
<td>20</td>
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<tr>
<td>04.1.2.7 Candied fruit</td>
<td>40</td>
</tr>
<tr>
<td>04.1.2.8 Fruit preparations, including pulp, purees, fruit toppings and coconut milk</td>
<td>20</td>
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<tr>
<td>04.1.2.9 Fruit-based desserts, including fruit-flavoured water-based desserts</td>
<td>20</td>
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<tr>
<td>04.1.2.10 Fermented fruit products</td>
<td>20</td>
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<tr>
<td>04.1.2.11 Fruit fillings for pastries</td>
<td>20</td>
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<tr>
<td>04.1.2.12 Cooked fruit</td>
<td>20</td>
</tr>
<tr>
<td>04.2.2.1 Frozen vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds</td>
<td>20</td>
</tr>
<tr>
<td>04.2.2.2 Dried vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds</td>
<td>20</td>
</tr>
<tr>
<td>Food Category No. and Food Category</td>
<td>Maximum Proposed Use-Level for Advantame (mg/kg)</td>
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<td>-----------------------------------</td>
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<tr>
<td>04.2.2.3</td>
<td>Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds in vinegar, oil, brine, or soybean sauce</td>
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<tr>
<td>04.2.2.4</td>
<td>Canned or bottled (pasteurized) or retort pouch vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds</td>
</tr>
<tr>
<td>04.2.2.5</td>
<td>Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g., peanut butter)</td>
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<tr>
<td>04.2.2.6</td>
<td>Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed pulps and preparations (e.g., vegetable desserts and sauces, candied vegetables) other than food category 04.2.2.5</td>
</tr>
<tr>
<td>04.2.2.7</td>
<td>Fermented vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera) and seaweed products, excluding fermented soybean products of food categories 06.8.6, 06.8.7, 12.9.1, 12.9.2.1 and 12.9.2.3</td>
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<tr>
<td>04.2.2.8</td>
<td>Cooked or fried vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), and seaweeds</td>
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<tr>
<td>05.0 Confectionery</td>
<td></td>
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<tr>
<td>05.1.1</td>
<td>Cocoa mixes (powders) and cocoa mass/cake</td>
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<tr>
<td>05.1.2</td>
<td>Cocoa mixes (syrups)</td>
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<td>05.1.3</td>
<td>Cocoa-based spreads, including fillings</td>
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<td>05.1.4</td>
<td>Cocoa and chocolate products</td>
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<tr>
<td>05.1.5</td>
<td>Imitation chocolate, chocolate substitute products</td>
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<td>05.2.1</td>
<td>Hard candy</td>
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<td>05.2.2</td>
<td>Soft candy</td>
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<tr>
<td>05.2.3</td>
<td>Nougats and marzipans</td>
</tr>
<tr>
<td>05.3</td>
<td>Chewing gum</td>
</tr>
<tr>
<td>05.4</td>
<td>Decorations (e.g., for fine bakery wares), toppings (non-fruit) and sweet sauces</td>
</tr>
<tr>
<td>06.0 Cereals and cereal products, derived from cereal grains, from roots and tubers, pulses and legumes, excluding bakery wares of food category 07.0</td>
<td></td>
</tr>
<tr>
<td>06.3</td>
<td>Breakfast cereals, including rolled oats</td>
</tr>
<tr>
<td>06.5</td>
<td>Cereal and starch based desserts (e.g., rice pudding, tapioca pudding)</td>
</tr>
<tr>
<td>07.0 Bakery wares</td>
<td></td>
</tr>
<tr>
<td>Food Category No. and Food Category</td>
<td>Maximum Proposed Use-Level for Advantame (mg/kg)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>07.1 Bread and ordinary bakery wares</td>
<td>80</td>
</tr>
<tr>
<td>07.2 Fine bakery wares (sweet, salty, savoury) and mixes</td>
<td>34</td>
</tr>
<tr>
<td>09.2 Processed fish and fish products, including molluscs, crustaceans, and echinoderms</td>
<td>15</td>
</tr>
<tr>
<td>09.3 Semi-preserved fish and fish products, including molluscs, crustaceans, and echinoderms</td>
<td>6</td>
</tr>
<tr>
<td>09.4 Fully preserved, including canned or fermented fish and fish products, including molluscs, crustaceans, and echinoderms</td>
<td>6</td>
</tr>
<tr>
<td>10.0 Eggs and egg products</td>
<td></td>
</tr>
<tr>
<td>10.4 Egg-based desserts (e.g., custard)</td>
<td>20</td>
</tr>
<tr>
<td>11.0 Sweeteners, including honey</td>
<td></td>
</tr>
<tr>
<td>11.4 Other sugars and syrups (e.g., xylose, maple syrup, sugar toppings)</td>
<td>60</td>
</tr>
<tr>
<td>11.6 Table-top sweeteners, including those containing high-intensity sweeteners</td>
<td>GMP</td>
</tr>
<tr>
<td>12.0 Salts, spices, soups, sauces, salads, protein products (including soybean protein products) and fermented soybean products</td>
<td></td>
</tr>
<tr>
<td>12.2.2 Seasonings and condiments</td>
<td>40</td>
</tr>
<tr>
<td>12.3 Vinegars</td>
<td>60</td>
</tr>
<tr>
<td>12.4 Mustards</td>
<td>7</td>
</tr>
<tr>
<td>12.5 Soups and broths</td>
<td>3</td>
</tr>
<tr>
<td>12.6 Sauces and like products</td>
<td>7</td>
</tr>
<tr>
<td>12.7 Salads (e.g., macaroni salad, potato salad) and sandwich spreads excluding cocoa- and nut-based spreads of food categories 04.2.2.5 and 05.1.3</td>
<td>20</td>
</tr>
<tr>
<td>13.0 Foodstuffs intended for particular nutritional uses</td>
<td></td>
</tr>
<tr>
<td>13.3 Dietetic foods intended for special medical purposes (excluding products of food category 13.1)</td>
<td>20</td>
</tr>
<tr>
<td>13.4 Dietetic formulae for slimming purposes and weight reduction</td>
<td>16</td>
</tr>
<tr>
<td>13.5 Dietetic foods (e.g., supplementary foods for dietary use) excluding products of food categories 13.1 - 13.4 and 13.6</td>
<td>20</td>
</tr>
<tr>
<td>13.6 Food supplements</td>
<td>110</td>
</tr>
<tr>
<td>14.0 Beverages, excluding dairy products</td>
<td></td>
</tr>
<tr>
<td>14.1.3.1 Fruit nectar</td>
<td>12</td>
</tr>
<tr>
<td>14.1.3.3 Concentrates for fruit nectar</td>
<td>12</td>
</tr>
<tr>
<td>14.1.4 Water-based flavoured drinks, including &quot;sport,&quot; &quot;energy,&quot; or &quot;electrolyte&quot; drinks and particulated drinks</td>
<td>12</td>
</tr>
<tr>
<td>Food Category No. and Food Category</td>
<td>Maximum Proposed Use-Level for Advantame (mg/kg)</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa</td>
<td>12</td>
</tr>
<tr>
<td>14.2.7 Aromatized alcoholic beverages (e.g., beer, wine and spirituous cooler-type beverages, low alcoholic refreshers)</td>
<td>12</td>
</tr>
<tr>
<td>15.0 Ready-to-eat savouries</td>
<td>10</td>
</tr>
</tbody>
</table>